1999053

American Journal of Epidemiology

Vol. 151, No. 4
Printed in U.S.A.

LETTERS TO THE EDITOR

RE: "CONTROLS WHO EXPERIENCED HYPOTHETICAL CAUSAL INTERMEDIATES SHOULD NOT BE EXCLUDED FROM CASE-CONTROL STUDIES"

The discussion by Poole (1) of the discrepancies between studies of the association of colorectal tumors with tobacco use may lead some readers to misinterpret the problem. The relevant question is why studies of colorectal adenomas consistently find an association with tobacco use whereas studies of colorectal cancer do not. This difference seems paradoxical since most cancers are thought to originate from a preexisting adenoma.

Our experience with a multigroup case-control study that examined in parallel the risk factors for small adenomas, large adenomas, and cancers offers a possible explanation (2). The absence of an association between tobacco and colorectal cancers in case-control studies could be due to misclassification of the disease, which will bias the odds ratio toward 1 if such misclassification is unrelated to the exposure. Our study (2) and others (3) have clearly demonstrated a strong relation between the risk of small adenomas and tobacco use. In contrast, no such relation with tobacco has been demonstrated in case-control studies of cancer, whereas two cohort studies (one in men (4) and one in women (5)) have demonstrated an association with cancer only after a 25-year delay after exposure. Therefore, we concluded that tobacco is a risk factor only for small adenomas and does not influence later progression.

If most colorectal cancers arise from preexisting adenomas as is thought, one can consider all colorectal adenomas and adenocarcinomas as a single entity, i.e., colorectal neoplasms. In a case-control study of risk factors for colorectal neoplasms as a whole, the controls should properly exclude cases with any colorectal neoplasm, adenomas as well as cancers. Depending on the proportion of attributable cases misclassified as controls, the observed association for a given risk factor will be more or less biased toward the null. Thus, risk factors for large adenomas, such as alcohol (2) or obesity (6, 7), need not contribute to subsequent progression to be linked with cancer in case-control studies (8, 9), because the proportion of large adenomas in a non-endoscoped control group is smaller than the proportion of small adenomas. However, this observation does not indicate a requirement for exclusion of adenoma patients from a hypothetical control group to be compared with cancer patients. Such exclusion would likely not be feasible for a population-based study or lead to other biases (e.g., due to a high rate of refusing colonoscopy among population controls or self-selection of a health-conscious group among screening colonoscopy controls). Instead, we suggest that epidemiologists perform parallel case-control studies of cancer and both small and large adenomas within the same population, using appropriate controls for each study (endoscoped controls for adenoma cases and population controls for cancer), or at least to interpret their results in this context. As colorectal cancer remains one of the leading cancers in western countries, proper interpretation of case-control data can contribute to designing preventive interventions that correctly target specific steps of the adenoma-carcinoma sequence.

REFERENCES

1. Poole C. Controls who experienced hypothetical causal intermediates should not be excluded from case-control studies. Am J Epidemiol 1999;150:547–51.
2. Boutron MC, Faivre J, Dop MC, et al. Tobacco, alcohol and colorectal tumors: a multistep process. Am J Epidemiol 1995; 141:1038–46.
3. Kikendall JW, Bowen PE, Burgess MB, et al. Cigarettes and alcohol as independent risk factors for colonic adenomas. Gastroenterology 1989;97:660–4.
4. Giovannucci E, Rimm EB, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in US men. J Natl Cancer Inst 1994;86: 192–9.
5. Giovannucci E, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in US women. J Natl Cancer Inst 1994;86: 183–91.
6. Bayerdörffer E, Mannes GA, Ochsenkühn T, et al. Increased risk of 'high risk' colorectal adenomas in overweight men. Gastroenterology 1993;104:137–44.
7. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
8. Longnecker MP, Orza MJ, Adams ME, et al. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1990;1:59–68.
9. LeMarchand L, Wilkens LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. Cancer Causes Control 1994;3:349–54.

Marie-Christine Boutron-Ruault
ISTNA-CNAM
2 rue Conté
75003 Paris, France

Charles S. Rabkin
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Bethesda, MD 20892

RE: "ALCOHOL INTAKE ASSESSMENT: THE SOBER FACTS"

Feunekes et al. (1) compared a number of methodological studies on alcohol assessment published after 1984. They found reasonable estimates for ranking individuals according to intake to justify the use of standard instruments for